Japan Pharmaceutical Manufacturers Association
Nihonbashi Life Science Bldg., 2-3-11, Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-0023 Japan
TEL: 81-3-3241-0340 FAX: 81-3-3242-1767

APAC Access To Innovative Medicine Task Force (ATIM TF) Activity Report

2020 APAC ATIM Theme: Consideration of merging ICH M9 BCS for the BE (Bioequivalence) waiver for the new drug application and post-approval changes

Japan Pharmaceutical Manufacturing Association (JPMA)
APAC ATIM Task Force
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Due to the global spreading of COVID-19 occurred in the spring of 2020, 9th APAC meeting in Tokyo has been cancelled. In this document, JPMA ATIM Task Force summarize the activities and selection BCS for the theme of APAC 2020.

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1 Background and introduction on the new theme for 2020 APAC ATIM session.

At 8th APAC meeting, ATIM have issued a position paper to outline the goal and achievements of the taskforce in alignment with APAC mission[1].

1 - 1 ATIM mission and the position of JPMA ATIM TF

In 2019, JPMA issued a position paper for the continuing activities in pursue APAC missions. As a member for the APAC, ATIM taskforce proposes the following recommendations for the post approval change procedure and reduce burden for conducting most time limiting stability studies while keeping regulatory science justification. Innovative medicines of comparable or improved quality can be supplied in a more efficient manner by:

[1] APAC Participating Countries Position paper on efficient CMC/GMP for Access To Innovative Medicine, issued and presented at 8th APAC meeting, Tokyo 2019

1) Introduce science and risk based approach for post approval change process.
2) Implement mutual understanding and commitment approach for change management using the tools such as Post-Approval Change Management Protocol (PACMP) and Biopharmaceutics Classification System (BCS).
3) Increase opportunities for dialogue and collaboration between industry and regulators to discuss integrated science and risk based approaches to stability

ATIM TF, together with other members from JPMA, is currently considering various approaches for the faster approval medicines including post approval changes and for the secured supply and we will continue to listen and search for the ways to achieve the APAC missions.

1 - 2 Background for selecting 2020 Theme

For selecting the 2020 theme, ATIM TF have decided to pursue the topics on the "Industry Perspective For Convergence Of Post-Approval Change Procedure" and considered following 4 points;

- Introduce **science- and risk-based approach** for change review process for efficient use of resources such in WHO guideline
- Seek an opportunity to **adopt ICH Q1A stability approach** to enhance and promote continuous improvement of the product and lower the level of introducing new innovative medicine to the patient
- Consider to implement **mutual understanding and commitment approach**, to conduct efficient stability and change management, using the tools such as Post-Approval Change Management Protocol (PACMP)
- Examine Support Biopharmaceutics Classification System (BCS) of drug substance and provide recommendation to **support waiver of bioequivalence studies**

Among the four points considered, we have decided to focus on the BE (bioequivalence) study. As a part of the activity, the TF clarified each associations' requirement for the BE study for the post approval changes of innovative medicines and consider the merging ICH guide, ICH M9, to discuss on the BCS and biowaiver acceptable to each of the association.

1 - 3 Issue and Challenges

From 2017 survey conducted in JPMA participating companies, there were responses where at the time of submitting post-approval change, anonymous regulatory agencies have requested to conduct Bioequivalent (hereafter refer to as BE) study for the proposed change, where for the same change, BE was not required in US or EU regulatory agencies[2]. Although it is understandable that an agency have requested to conduct the BE study considering the safety and the risk associated with the proposed change by the company, this unique requirement delayed the delivery of the new drug or quality improved drug product for the patients and more robust supply chain to the one's nation.

During the theme selection for 9th APAC, ATIM TF considered to uptake merging ICH guideline, ICH M9, on the BE waiver using BCS. This new ICH guideline discusses technical and criteria for the determination of Class I and III immediate release solid dosage form.

The intent of selecting this theme is to enhance the following points;

- Introduction of harmonized BE biowaiver will **reduce unnecessary clinical study** and may proceed efficient change control procedure based on in vitro

[2] Presentation from JPMA at 7th APAC ATIM session

- Conducting unique BE study will bring additional time and cost of the drug, which will be reflected to the pricing of the product that may not be beneficial for the patients
- **Immediate release solid dosage drug is a better way to bring the drug product to the patient** who needs drugs but may have difficulty to visit hospitals periodically and this is a formulation that has been most prescribed form of the drug product. Implement and promote biowaiver based on science base
- Although ASEAN Guideline for the Conduct of BE Studies (Final: Mar. 2015) exist to present BE/BA test, however, there is no clear BE Biowaiver ASEAN Guideline in Asia
- Introduce BCS -based Biowaiver (ICH M9) and promote within Asia?

2 Activities

For the agreed theme, the taskforce have studied the issue and challenges exist among APAC participating members to understand the current existing document and the contents therein and possibility to work on the adaptation of new technical ICH guideline for the faster delivery of the innovative drug.

2 - 1 Basic Understanding of Biowaiver

The relation between BE and BCS is the following;

The safety of the drug associated with clinical study is secured through in vivo and vitro study. During the development of the drug, the areas of the safety is proven by the clinical study, clinical study and by in-vitro bioequivalence in some area of the drug. The Figure 1 shows the relationship between in vivo dissolution and in vitro bioequivalency.

To find the medical effect of the candidate compound, it is necessary to obtain equivalent drug concentration profile at the point of action. To surrogate the point of action, in vivo study determines the equivalence of the drug in blood concentration (in vivo BE Study). Further, the blood concentration profile equivalency depends on the dissolution rate of the drug substance in the digestive tract, it is possible that this rate could be assured by dissolution study. For the sake of this report, the focusing area of the drug development is limited immediate release-oral solid dosage drug (figure 1).

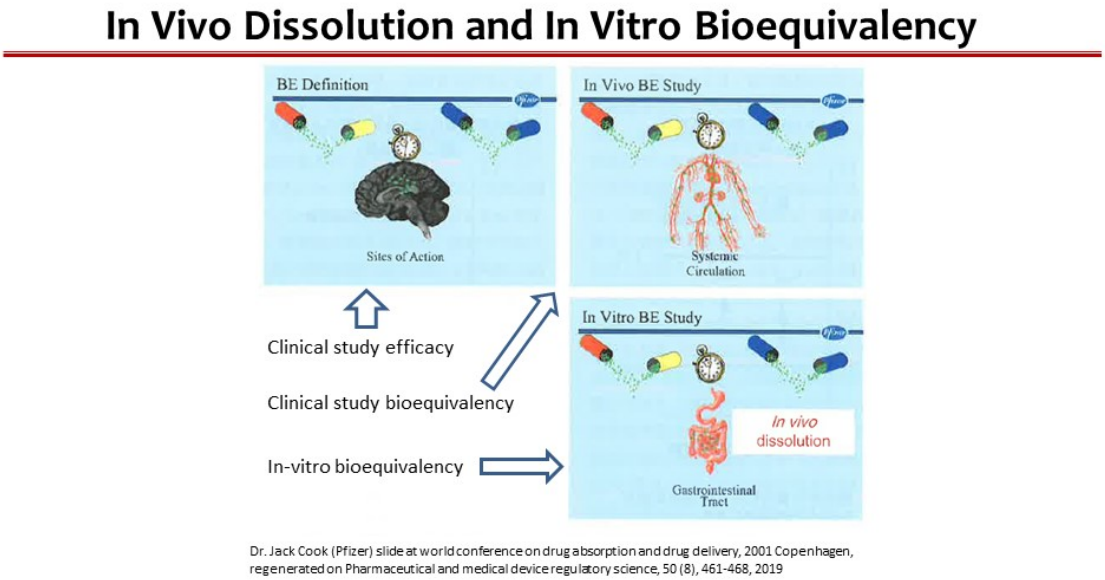

Figure 1: In vivo and in vitro bioequivalency

When this concept is applied for the branded drug, its relation is shown in Figure 2. To improve the access to the new drug and to aid the stable supply of the drug, it is often the case the company makes modification to the formulations or make manufacturing process. If the product market expands, it is necessary to add manufacturing sites, and/or scale-up the production. To prove that the effectiveness of the drug product remains the same before and after the changes, in some case, it is necessary to prove that the blood concentration profile is equivalent through bioequivalency test or dissolution test.

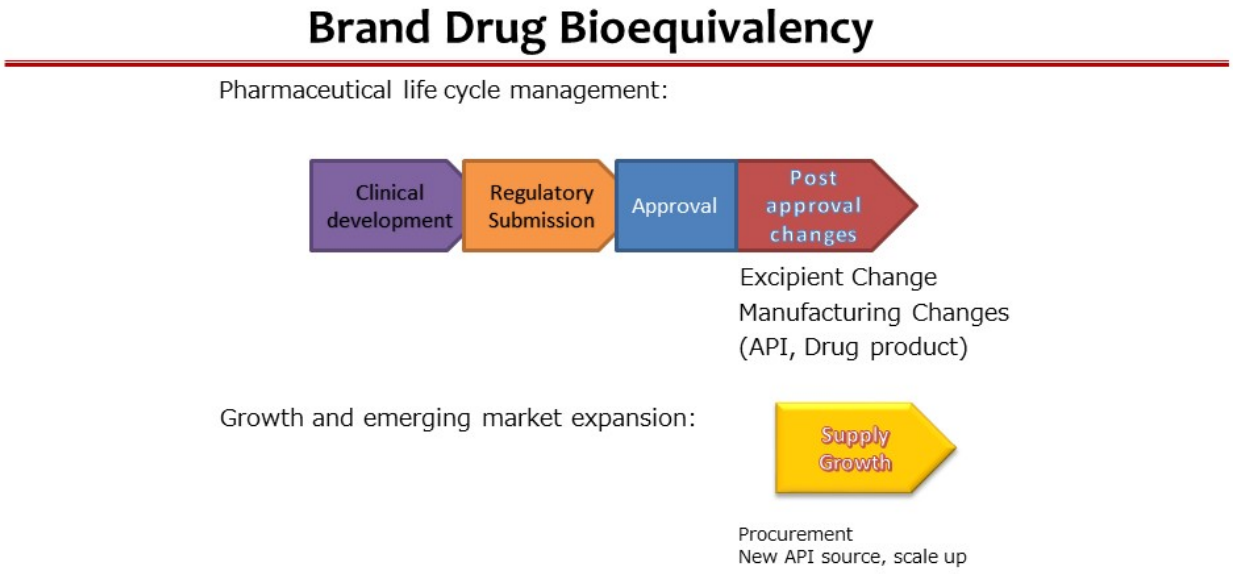

Figure 2: Brand drug equivalency

2 - 2 Expectation of BCS BE Biowaiver

In 2017, US-FDA published an article to review the progress and application results of using BCS guideline to share the FDA's current thinking on areas of improvement of this guidance[3]. During the period between 2004 and 2017, >160 applications were approved, or tentatively approved, based on the BCS approach across multiple therapeutic areas. According the past US FDA record, at least 50% of these approvals were in the central nervous system (CNS) area. These findings indicate a robust utilization of the BCS approach toward reducing unnecessary in vivo BE studies and speeding up availability of high quality pharmaceutical products.

[3] *Mol. Pharmaceutics* **2017,** 14, 4334-4338. DOI:10.1021/acs.molpharmaceut.7b00687 Copyright © 2017 American Chemical Society

Impact of the US FDA "Biopharmaceutics Classification System" (BCS) Guidance on Global Drug Development

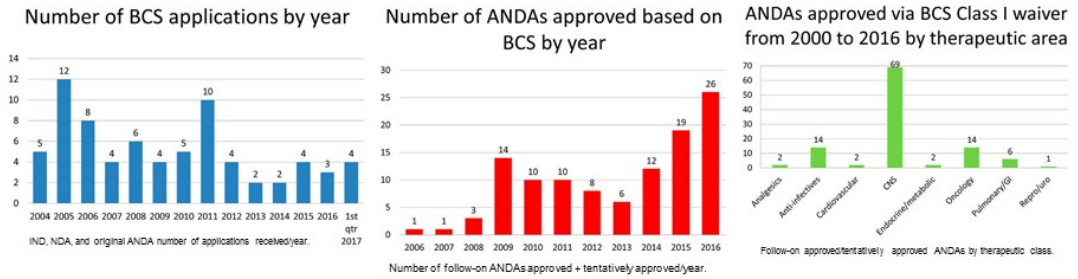

Table 1. BCS Class 1 Applications Received and Approved for New and Generic Drugs from 2004 to March 2017

type of application	new drug		generic drug
# applications	48		25
# approved (% of total)	28 (58%)		23 (92%)
	IND stage	NDA stage	
# applications	18	30	
# approved (% of total)	12 (67%)	16 (53%)	

Published in: Mehul U. Mehta; Ramana S. Uppoor; Dale P Conner; Paul Seo; Jayabharathi Vaidyanathan; Donna A. Volpe; Ethan Stier; Dakshina Chilukuri; Angelica Dorantes; Tapash Ghosh; Haritha Mandula; Kimberly Raines; Pariban Dhanormchitphong; Janet Woodcock; Lawrence X Yu;
Mol. Pharmaceutics **2017,** 14, 4334-4338.
DOI: 10.1021/acs.molpharmaceut.7b00687

Figure 3: Impact of the US FDA BCS guideline on global drug development

In the article, the USFDA conclude the survey as success of new BCS guidance is indicated in several ways:

A) On cost, the guidance has saved the industry in excess of $100 million. This estimate is arrived at using the method utilized by Cook *et al* and using the number of approvals summarized in this article;

B) Several other agencies across the globe have issued their version of the BCS guidance. EMA formalized its position on BCS in 2010, ANVISA (Brazil) in 2011, and Health Canada has come out with their final position in 2014. Perhaps the greatest impact has been seen by the utilization of this approach by the WHO which has created its Essential Medicines list and several of these products are approved based on the BCS principles across many parts of the world where there is limited regulation; and

C) A very large number of human subjects have been spared from being subjected to unnecessary BE trials

The survey conducted by US FDA is encouraging to justify the success of implementing the BCS for the BE biowaiver, not only from the risk of subjecting a body of patients to subject for the unnecessary BE trials, but from the perspective of the product development, this will reduce the finance and time burden for the development of the new innovative drug. Also the article shows that there are some limitation for the use of BCS to classify the classification of BE biowaiver, but this method is not limited to approve the generic drug, but can also support the development of the new drug product as well.

2 - 3 Existing Guidelines

The new ICH guideline, ICH M9 was developed to aim address BCS-based biowaiver. The guideline provides recommendations to support the biopharmaceutics classification of medicinal products and the drug substance therein, to provide recommendations to support

the waiver of bioequivalence studies[4]. The guideline is now adopted by ICH management committee to reach Step 4 of the approval steps in the hope to result in the harmonization of current regional guidelines/guidance and support streamlined global drug development. This guideline will guide in the BE biowaiver applicable to Class I and III and their technical harmonization of the techniques to converge the regulation (Figure 4).

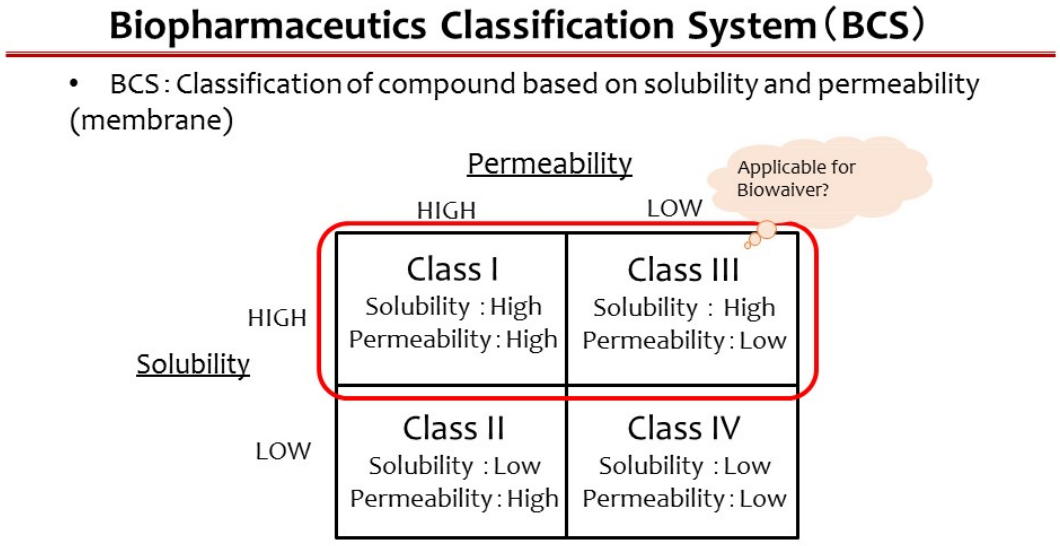

Figure 4: Biopharmaceutical classification system in ICH M9

The concept and implementation of BCS based biowaiver is not new. Globally, there are various guidelines exist to guide the implementation of the using of BCS for the biowaiver. The listing of examples are given in figure 5.

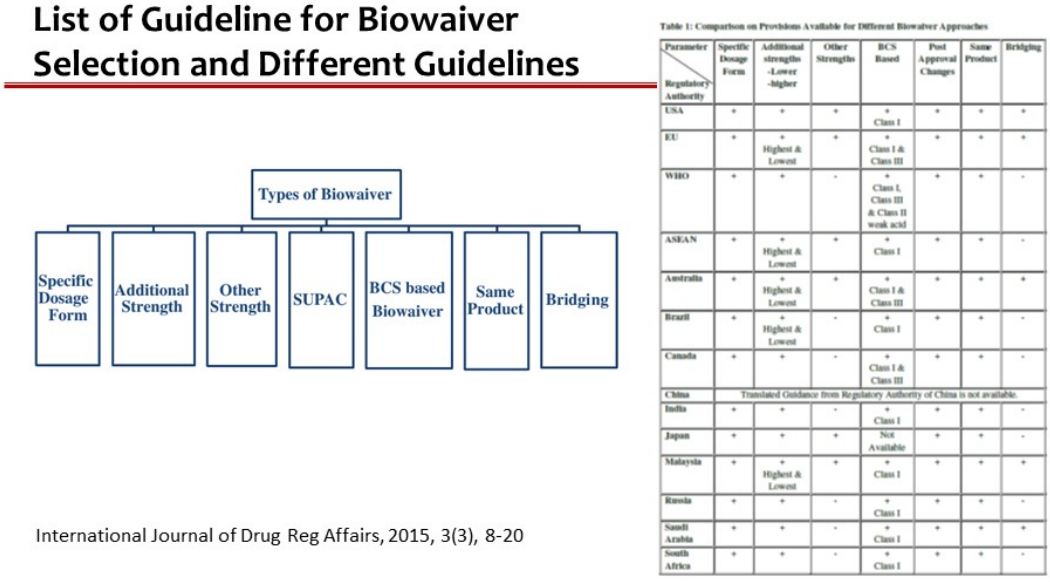

Figure 5: List of Guidelines for biowaiver

[4] Final endorsed Concept Paper M9: Biopharmaceutics Classification System-based Biowaivers, 7 October 2016

There are various guidelines that discusses BE biowaiver by the use of BCS. These guidelines are similar but are not fully aligned in the following points

- It is necessary to converge the principals for Biowaiver (Biopharmaceutical Classification and standard for administration change)
- It is necessary to converge the data required for BCS classification and evaluation method

When the existing guideline is compared to the new ICH M9 guideline, there are some differences where everyone has an area that need to adopt or need to work on. As an example, table 1 highlight some of the differences between ASEAN guideline and the ICH M9 guideline.

Table 1: Comparison between ICH M9 and current ASEAN Guideline for BCS Biowaiver

Item	ICH M9(Step 4)	ASEAN BE GUIDELINE
Scope	•Immediate release, solid orally administered dosage forms or suspensions, Fixed-dose combination (FDC) products •Non-narrow therapeutic Index (Deliver drug to the systemic circulation)	•Immediate release, solid pharmaceutical product, Fixed-dose combination (FDC) products •Non-narrow therapeutic Index (Deliver drug to the systemic circulation)
Solubility (API)	Class I and Class III •High solubility[1)] •pH1.2-6.8(1.2, 4.5, 6.8), 37ºC •Shake-flask method, •Timeframe: duration of absorption	Class I •High solubility[1)] •pH1-6.8(1.2, 4.5, 6.8), 37ºC •Shake-flask method
Permeability	Class I •Absolute BA≥85%(in vivo) or Caco-2 cell: high permeability Class III •Absolute BA<85%(in vivo) or Caco-2 cell: not high permeability	Class I •Absolute BA≥85%(in vivo) Class III •Not described
Salt	Not described	Class I •Different salt is applicable
Dissolution	Class I • ≥ 85% within 15min or ≥ 85% within 30min and similar dissolution profile Class III • ≥ 85% within 15min	Class I • ≥ 85% within 15min or ≥ 85% within 30min and similar dissolution profile Class III •Not described
Excipient	Class I •Excipients may affect absorption[2)]: same quality and similar quantity within 10% Class III •All excipients: same quality and similar quantity within 10%	Class I •All excipients: same quality and similar quantity •Excipients may affect absorption[2)]: same quality and quantity Class III •Not described

1) High solubility: highest single dose is completely soluble in 250mL
2) Excipients may affect absorption: mannitol, sorbitol, and surfactants

To summarize the points, the new ICH M9 guideline focuses on the following areas;

- Approval of Formulation Change in Drug Product
  - Use of clinical data (in vivo) to assure the product reliability
  - Conduct Bioequivalence (BE) by human
- Waiver of BE test (Biowaiver)
  - Use physical property data of API and quality attribute of the drug product→ Potential acceptance of the used of *in vitro data* to assure the change
- Biopharmaceutics Classification System (BCS)
  - Could be applied for Class I and Class III

2-4 Survey on the consideration of BCS BE biowaiver from the APAC participating members

To further understand the current BCS BE biowaiver situation in APAC participating members and also from the industrial perspective, JPMA have conducted a survey to both parties among the participating members. The details from the survey is given in the appendix. In general, no BE change is required for minor proposed changes, but may require BE if the change impacts BA of the drug. Unfortunately, there is no certain conclusion obtained from this survey as this was a focusing point of the panel discussion during the APAC ATIM session.

It was planned that at the APAC ATIM session, following discussions were planned for the better understanding of how BE Biowaiver approaches are implemented and the next steps for the adaptation of the ICH M9 guidelines.

To encourage scientific and risk based approach to Bioequivalence (BE) Studies for post approval change (PAC) in "your Country/ Region" in the present status,
Question 1: Have you ever applied "BCS-based Biowaiver approach" * for the PAC (ex. formulation change or manufacturing site change) of branded (new) drugs? (Yes or No)
**** "BCS-based Biowaiver approach" means in vivo bioequivalence studies is not required by this approach.***

ICH-M9 guideline (BCS Biowaiver) was agreed among major regulatory agencies at the Singapore meeting in Nov.2019.
Question 2: Does your country has a plan to expand the application of "BCS based biowaiver approach" following to the ICH recommendation in the future? (Yes or No)

2-5 Current situation in Japan and perspectives from PMDA

To share the situation in Japan, the taskforce seek current situation in Japan to share with the APAC participating members. For the discussion, Dr. Ryosuke Kuribayashi, PMDA, also a member of ICH M9 from PMDA have agreed to participate for the discussion and share the current situation in Japan. On March 2020, MHLW in Japan have published the revision of Japanese BE guideline to address the following points;

- Addition of fed State BE study
- Reconsideration the pilot study and add-on study
- Acceptance the foreign subject in BE study
- Clarification on the requirement of reference product

Addition of fed State BE study

Until the revision is made, the PMDA required the fed state BE study only for the extended release products. After the revision of the BE guidelines, for Japan, fed state BE study is now requesting for the type of products including the followings.

- Solubility improvement products, such as solid dispersion, microemulsion, amorphous, and nano particle products

The reason to include this criteria is for the products that are design to improved solubility of the products with a function to improve the solubility to assure the bioequivalence of the product functions. This may be applicable to the products that have special controlled release mechanism and product design under the severe condition.

- Enteric-coated products, such as delay release products

The reason to include this criteria due to have a concern on the possibility that have the drug concentration-time profiles that may have different due to the difference of gastrointestinal transit time difference between generic and original products.

Although the criteria of enteric-coated product is to target the same profile between original and generic drug, the similar principle can be applied when changing the formulation of the original drug to different formulation as part of active product improvement. The comparison of the equivalency of the original drug to the modified/generic drug is particularly important to consider the state of food induced effect to GI such as changeing the intragastrtic pH. The change in the intragasteric pH will promote the secretion bile acid and enzyme and also promote the digestion of drug products (destruction and crush). Consequently, this will impact the solubility of the API by meals and delay the gastric emptying rates.
With the revised BE guideline, PMDA incorporated the interim analysis for BE study and sample size re-estimation. When subject for the BE study, the sponsors must plan the methodology in order to control Type-I error rate 5% or less.

Acceptance the foreign subject in BE study
In the revised BE guideline, it is also considered for the applicability of the data of bioequivalence study. In conclusion, it is now consider that the data from the foreign subject are scientifically acceptable, however, during the study, if significant dissolution between two products are observed, the subject for BE study should be focused on the Japanese population. To avoid the doubt of the data, PMDA have highly recommended the discussion at the level of face-to-face consultation.

Clarification on the requirement of reference product
When applying the BE biowaiver in Japan, it is important to note that the drug need to use domestic original product is required as a reference product for BE evaluations. This decision is strongly tied to the legal aspects.

2 - 6 Recommendation and Proposals

There are several points that may lead to the following points to consider the benefit of applying new ICH guideline;

- BE biowaiver based on BCS can contribute the faster development, avoid unnecessary exposure of healthy patient during BE, and efficient review of formulation change in pre- and post- submission
- Adaptation of the concept and risk based approach, this may also reduce the

financial impact of the drug development by the industry, consequently the region may benefit from the faster introduction on the innovative drug with less pricing burden

- With development ICH guideline, how can we adopt new BCS and its method, to harmonize the procedure to adopt BCS approvals

Considering these points, ATIM taskforce was willing to hear the voices from the participating members to adopt the new ICH M9 guideline and also to discuss the means to align the concept of applying scientific risk-based approach to introduce the concept of new ICH guideline.

3 Next Step

For the proposal from ATIM TF, it is recommended that we need further discussion for better understanding of the how BCS could be used and benefit for the faster delivery of innovative drug and also how to implement this concept without reaching a consensus to adopt the agreement.

In addition, the topic also raises in the following areas;

- According to the survey from the participating members, whether to apply BCS biowaiver is depended on the classification of the changes proposed during the time of post-approval change
- As presented by BE biowaiver guideline revision, BE biowaiver also need to consider the fed state study for other oral drug as raised in the ICH M13 (bioequivalence for immediate release solid oral dosage forms). As indicated, identify current gap and find a way for convergence may have easier to adopt the new merging guidelines in this focusing area. How should we prepare for this?

Further information sharing and discussion to prepare for the next APAC meeting may have an answer to resolve these points.

Other supportive activities done by the APAC ATIM TF in 2019

- **Thai FDA adopts Japanese Pharmacopoeia (JP) as a reference pharmacopoeia** The Notification will become effective on 26 January 2020. (https://www.bakermckenzie.com/en/insight/publications/2019/08/japanese-pharmacopoeia-announced-by-thai-fda)
- **Indonesian Health Authorities announced to include Japan as a reference country for 120 days evaluation path for new drug** (https://www.mhlw.go.jp/stf/newpage_05934.html)
- **PMDA-ATC Pharmaceuticals Review Seminar 2020 in Jakarta, Indonesia** (https://www.pmda.go.jp/english/symposia/0164.html)